REMARKS

I. Status of the Claims

With the amendments provided herein, claims 23-24, 28, and 31 are pending. Claims 1-22 were previously canceled in the Preliminary Amendment filed June 29, 2006. Claims 25-27, 29-30, and 32-42 are canceled herein without prejudice or disclaimer. Claims 23, 24, and 28 have been amended herein. Claim 23 has been amended to incorporate the limitations of claim 27 (which has subsequently been canceled). Support for this amendment can be found in the specification and claims as-filed. *See, e.g.,* original claim 5. Further, claim 23 has been amended to recite "R_4 is chosen from phenyl, (C_1-C_{20})-alkylphenyl, and *(C_2-C_{20})-alkyl.*" Currently Amended Claim 23, emphasis added. Support for this amendment also can be found in the specification and claims as-filed. *See, e.g.,* specification at page 6, lines 18-24, reciting "ethyl..." and such as examples of alkyl radicals. Finally, claim 23 has been amended to delete the phrase "in all ratios" and the term "hydrates." Claim 24 has been amended to limit R_{11} to methyl. Support for this amendment can be found in the specification and claims as-filed. *See, e.g.,* original claim 2. Claim 28 has been amended to be dependent upon amended claim 23, rather than canceled claim 27. As such, no new matter has been added.

II. Rejection under 35 U.S.C. § 112, first paragraph

(a) Claims 32-42

Claims 32-42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the reasons set forth in the Office Action at pages 2-15.

Specifically, the Office admits that the specification is "enabling for an in vitro method of inhibiting NOS release by the compounds of Formula (I)." Office Action at page 2. However, the Office alleges that the specification "does not reasonably provide enablement for a method of treating a disorder associated with an increased NO level in a subject with compounds of Formula (I) (claims 32-39), where the disorder is selected from those characterized by pathological blood pressure decreases; inflammatory disorders; insulin-dependent diabetes mellitus; transplant rejection reactions; cardiovascular disorders; disorders of the nervous system/central nervous system; and kidney disorders (claim 40) where the subject is a mammal (claim 41) or a human (42)." *Id.* Applicants respectfully traverse. Nonetheless, solely to expedite prosecution, Applicants have deleted claims 32-42 herein. As such, Applicants respectfully request withdrawal of the rejection.

(b) Claims 23-42

Claims 23-42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the reasons set forth in the Office Action at pages 15-16. Specifically, the Office admits that the specification is "enabling for Formula I compounds, stereoisomeric and tautomeric forms and physiologically tolerated salts and esters thereof." Office Action at page 15. However, the Office alleges that the specification "does not reasonably provide enablement for their hydrates, or mixtures thereof in all ratios." *Id.* The Office states that "the numerous examples presented all fail to produce a hydrate. The evidence of the specification is clear: These compounds do not possess the property of forming hydrates; there is no evidence that such hydrates even exist." *Id.* The Office also claims that "[t]he recitation 'mixtures thereof in

all ratios' encompasses unsupported mixtures of claimed compounds and the recited forms; it should be singularized." *Id.* at page 16. Applicants respectfully traverse. Nonetheless, solely to expedite prosecution, Applicants have deleted the term "hydrates" from the claims and deleted the phrase "in all ratios," as required by the Office. Accordingly, Applicants respectfully request withdrawal of the rejection.

III. Rejection under 35 U.S.C. § 102

(a) U.S. Patent No. 4,746,659

Claims 23 and 31 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,746,659 ("the '659 patent") to DeGraw et al. for the reasons set forth in the Office Action at pages 16-17. Specifically, the Office alleges that the '659 patent "describ[es] 10-alkyl-10-deazaminopterins as anti-tumor agents" and notes "especially RN 102153-04-8...and RN 102153-05-9." Office Action at page 16. The Office further points to compounds in columns 1-3 "that [the '659 patent] acknowledges to be known in the prior art having anti-tumor activity." *Id.* at page 17. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted $(C_1\text{-}C_5)$-alkyl. However, the compounds of the '659 patent have a hydrogen atom at the R_{11} position. Claim 31 depends upon claim 23 and thus incorporates the same limitations. As such, claims 23 and 31 are not anticipated by the '659 patent. Accordingly, Applicants respectfully request withdrawal of the rejection.

(b) Nair

Claims 23 and 31 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by J. Org. Chem., 1985, 50, 1879-1884 to Nair ("Nair") for the reasons set forth in the Office Action at page 17. Specifically, the Office alleges that Nair "describ[es] RN 96056-44-9...and RN 96056-45-0." Office Action at page 17. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted (C_1-C_5)-alkyl. However, the compounds of Nair have a hydrogen atom at the R_{11} position. Claim 31 depends upon claim 23 and thus incorporates the same limitations. As such, claims 23 and 31 are not anticipated by Nair. Accordingly, Applicants respectfully request withdrawal of the rejection.

(c) Taylor et al.

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by J. Am. Chem. Soc., 1973, 95(19), 6413-18 to Taylor et al. ("Taylor et al.") for the reasons set forth in the Office Action at pages 17-18. Specifically, the Office alleges that Taylor et al. "describ[e] RN 50691-64-0." Office Action at page 17. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted (C_1-C_5)-alkyl. However, the compounds of Taylor et al. have a hydrogen atom. Other compounds of Taylor et al. possess a double bond at the 7,8-position of the pteridine ring system, which falls outside Formula (I) of claim 23. As such, claim 23 is not anticipated by Taylor et al. Accordingly, Applicants respectfully request withdrawal of the rejection.

(d) Beilstein Record 5633531 dated February 12, 1993

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Beilstein Record 5633531 dated February 12, 1993 ("B.R. '531") for the reasons set forth in the Office Action at page 18. Specifically, the Office alleges that B.R. '531 "describ[es] 4-[1-(2,4-diamino-7,8-dihydro-pteridin-6-ylmethyl)-propyl]-benzoic acid." Office Action at page 18. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted $(C_1\text{-}C_5)$-alkyl. However, the compound of B.R. '531 has a hydrogen atom at the R_{11} position. As such, claim 23 is not anticipated by B.R. '531. Accordingly, Applicants respectfully request withdrawal of the rejection.

(e) Beilstein Record 5613739 dated February 12, 1993

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Beilstein Record 5613739 dated February 12, 1993 ("B.R. '739") for the reasons set forth in the Office Action at page 18. Specifically, the Office alleges that B.R. '739 "[d]escribe[s] 4-[2-(2,4-diamino-7,8-dihydro-pteridin-6-yl)-ethyl]-benzoic acid." Office Action at page 18. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted $(C_1\text{-}C_5)$-alkyl. However, the compound of B.R. '739 has a hydrogen atom at the R_{11} position. As such, claim 23 is not anticipated by B.R. 739. Accordingly, Applicants respectfully request withdrawal of the rejection.

(f) Beilstein Record 1117249 dated November 29, 1988

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Beilstein Record 1117249 dated November 29, 1988 ("B.R. '249") for the reasons set

forth in the Office Action at pages 18-19. Specifically, the Office alleges that B.R. '249 describes "6-propyl-7,8-dihydro-pteridine-2,4-diamine." Office Action at page 18. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted (C_1-C_5)-alkyl. However, the compound of B.R. '249 has a hydrogen atom at the R_{11} position. As such, claim 23 is not anticipated by B.R. '249. Accordingly, Applicants respectfully request withdrawal of the rejection.

(g) Beilstein Records dated November 28, 1988

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Beilstein Records dated November 29, 1988 ("B.R. 11/29/88") for the reasons set forth in the Office Action at page 19. Specifically, the Office alleges that B.R. 11/29/88 describes:

- Beilstein Registry No. 521731, 6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 525714, 6,8-dimethyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 531116, 8-ethyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 532168, 8-isopropyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 551214, 8-benzyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 598897, N-{4-[(2,4-diamino-7,8-dihydro-pteridin-6-ylmethyl)-methyl-amino]-benzoyl}-glutamic acid;

- Beilstein Registry No. 599420, N-{4-[(2,4-diamino-8-methyl-7,8-dihydro-pteridin-6-ylmethyl)-methyl-amino]-benzoyl}-glutamic acid.

See Office Action at page 18. Applicants respectfully traverse.

With the amendments provided herein, R_4 of claim 23 is chosen from phenyl, (C_1-C_{20})-alkylphenyl, and (C_2-C_{20})alkyl, which is optionally substituted with -OH, (C_1-C_{20})-alkyloxy, or halogen. However, the compounds of B.R. 11/29/88 have other groups at the R_4 position which fall outside the scope of currently amended claim 23. Specifically, Beilstein Registry Nos. 521731, 525714, 531116, 532168, and 551214 have a methyl group at the R_4 position. Additionally, Beilstein Registry Nos. 598897 and 599420 have -$CH_2N(CH_3)$-C_6H_4-CO-NH-$CH(CO_2H)(CH_2CH_2CO_2H)$ at the R_4 position. Further, Beilstein Registry Nos. 521731 and 598897 have a hydrogen at R_{11}, which is limited to an optionally substituted (C_1-C_5)-alkyl in currently amended claim 23. As such, claim 23 is not anticipated by B.R. 11/29/88. Accordingly, Applicants respectfully request withdrawal of the rejection.

(h) Beilstein Records dated August 28, 1992

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Beilstein Records dated August 28, 1992 ("B.R. 8/28/92") for the reasons set forth in the Office Action at pages 19-20. Specifically, the Office alleges that B.R. 8/28/92 describes:

- Beilstein Registry No. 5108955, 2,4-diamino-8-benzyl-7,8-dihydro-6,7,7-trimethylpteridine; and
- Beilstein Registry No. 5032074, 2,4-diamino-7,8-dihydro-6,7,7-trimethylpteridine.

See Office Action at page 18. Applicants respectfully traverse.

With the amendments provided herein, R_4 of claim 23 is chosen from phenyl, (C_1-C_{20})-alkylphenyl, and (C_2-C_{20})alkyl, which is optionally substituted with -OH, (C_1-C_{20})-alkyloxy, or halogen. However, the compounds of B.R. 8/28/92 have a methyl group at the R_4 position. Additionally, Beilstein Registry No. 5032074 has a hydrogen at the R_{11} position, which is limited to an optionally substituted (C_1-C_5)-alkyl in currently amended claim 23. As such, claim 23 is not anticipated by B.R. 8/28/92. Accordingly, Applicants respectfully request withdrawal of the rejection.

(i) Zimmerman et al.

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by J. Med. Chem., 1977, 20(9), 1213-15 to Zimmerman et al. ("Zimmerman et al.") for the reasons set forth in the Office Action at page 20. Specifically, the Office alleges that Zimmerman et al. "describ[e] 7,8-dihydro-6,7-bis(1-methylethyl)-2,4-pteridinediamine." Office Action at page 20. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted (C_1-C_5)-alkyl. However, the compounds of Zimmerman et al. have a hydrogen atom at the R_{11} position. As such, claim 23 is not anticipated by Zimmerman et al. Accordingly, Applicants respectfully request withdrawal of the rejection.

(j) Kwee et al.

Claim 23 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Biochem. Biophys. Acta, 1973, 297(2), 285-96 to Kwee et al. ("Kwee et al.") for the reasons set forth in the Office Action at page 20. Specifically, the Office alleges that

Kwee et al. "describ[e] 7,8-dihydro-6,7-dimethyl-2,4-pteridinediamine." Office Action at page 20. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted $(C_1\text{-}C_5)$-alkyl. However, the compounds of Kwee et al. have a hydrogen atom at the R_{11} position. As such, claim 23 is not anticipated by Kwee et al. Accordingly, Applicants respectfully request withdrawal of the rejection.

(k) U.S. Patent No. 3,242,178

Claims 23, 24, and 31 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 3,242,178 ("the '178 patent") to Elion for the reasons set forth in the Office Action at page 20. Specifically, the Office alleges that the '178 patent "describ[es] 2,4-diamino-6-hydroxymethyl-7,8-dihydropteridine, found to inhibit biochemical synthesis of p-2-amino-4-hydroxypteridin-6-yl-methylamino-benzoylglutamic acid (folic acid)." Office Action at page 20. Applicants respectfully traverse.

With the amendments provided herein, R_{11} of claim 23 is limited to an optionally substituted $(C_1\text{-}C_5)$-alkyl. However, the compounds of the '178 patent have a hydrogen atom at the R_{11} position. Claims 24 and 31 depend upon claim 23 and thus incorporate the same limitations. As such, claims 23, 24 and 31 are not anticipated by the '178 patent. Accordingly, Applicants respectfully request withdrawal of the rejection.

IV. Rejection under 35 U.S.C. § 103

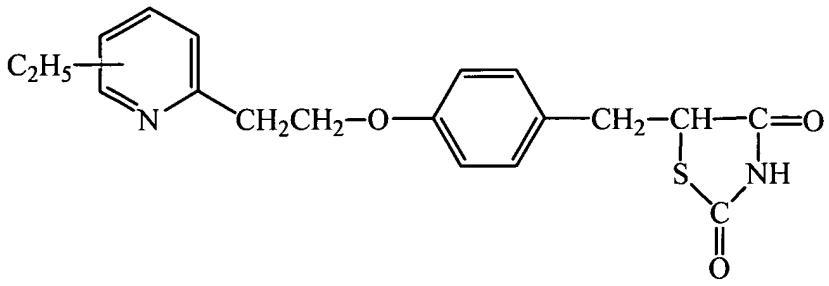
(a) EP '913

Claims 23, 27, 28, 31-33, 36, 37, and 40-42 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over EP 0 906 913 A1 ("EP '913") to Werner et al. for the reasons set forth in the Office Action at pages 21-23. Specifically, the Office alleges that EP '913 "describ[es] 1,2-Propanediol, 1-(2,4-diamino-1,7-dihydro-6-pteridinyl)-, (1R,2S)-...as an NO synthase inhibitor." Office Action at page 21. The Office claims that the compounds of EP '913 "render obvious lower alkyl homologs and position isomers thereof." *Id.* Further, the Office asserts that "[t]he skilled chemist would be well motivated to prepare other compounds and their compositions homologous and isomeric with those of [EP '913] according to the procedures taught therein with the expectation that such compounds would have the same activity." *Id.* at pages 21-22. The Office also claims that "the skilled practitioner would also be motivated to use such homologous and isomeric compounds and their compositions in methods of treating a disorder associated with an increased nitric oxide level." *Id.* at page 22. Applicants respectfully traverse.

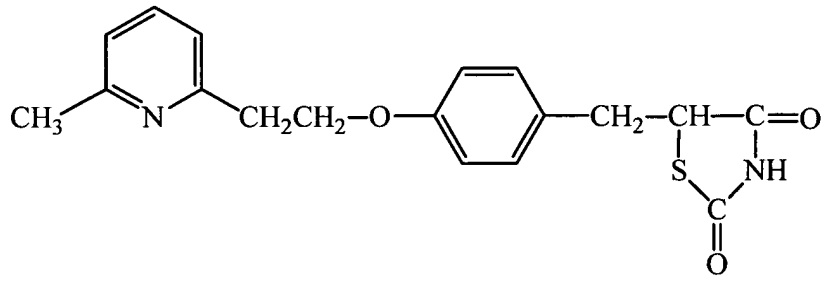
The Office claims that "[i]t has been held that compounds that are structurally homologous and isomeric to prior art compounds are *prima facie* obvious." *Id.* Applicants note, however, that compounds structurally homologous to those in the prior art, without more, are not *prima facie* obvious. As noted in M.P.E.P. § 2144.09(II), "[h]omology should not be automatically equated with *prima facie* obviousness." Indeed, the Federal Circuit has recently indicated that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a

showing of 'adequate support in the prior art' for the change in structure." *Takeda Chemical Ind. Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007) (internal citations omitted, underlining added).

In *Takeda*, the patented compounds had the general formula (claim 1):



The compound in the prior art, "compound b," had an identical formula to the patented compound, except that a methyl group, instead of an ethyl group, was attached to the pyridyl ring located on the left hand side of the molecule, as indicated in the drawing below. *Id.* at 1172.



Because the structure of the patented compounds allowed the substitution by the ethyl group on any available carbon atom in the pyridyl ring, the only difference between the prior art compound and the claimed compounds was a methylene group (–CH_2-) in the alkyl radical of the pyridyl ring[1]. The court in *Takeda* held that because there was

[1] The actual commercial embodiment marketed by the patentee (pioglitazone) was also claimed in a dependent claim, and had the structure shown below. It can be seen that the only differences between pioglitazone and compound b were the replacement of the (continued...)

no suggestion to prepare the claimed compounds in light of the prior art compound, the patented compounds were not obvious. *Id.* at 1776-77.

Applicants note that *Takeda* was decided after the landmark case of *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Accordingly, the *Takeda* court also considered in its decision the Supreme Court's guidelines enunciated in *KSR* regarding obviousness determinations. *Takeda*, 83 USPQ2d at 1174.

Summarizing the rationale behind its decision, the *Takeda* court explained that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new compound." *Id.* at 1774 (underlining added). The Office has not complied with this requisite.

Moreover, with the amendments provided herein, claims 27, 32-33, 36, 37, and 40-42 have been canceled making the rejection of these claims moot. Currently amended claim 23 limits, among other things, R_{11} to an optionally substituted (C_1-C_5)-alkyl. Claims 28 and 31 depend upon claim 23 and thus, encompass this same limitation. EP '913, by contrast, discloses only compounds bearing a hydrogen at the R_{11} position. Further, neither the Office nor EP '913 provide a reason to modify at R_{11} at all, let alone to an optionally substituted (C_1-C_5)-alkyl. Because the Office has not

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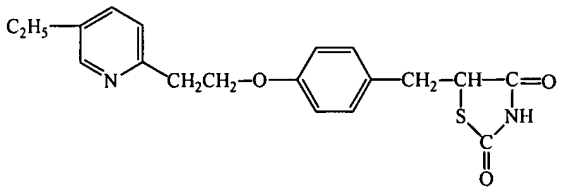
(...continued)
methyl group by an ethyl group and in the location of the ethyl group within the pyridyl ring. *Id.* at 1772.



complied with the explicit requirement enunciated in *Takeda* "to identify some reason that would have led a chemist to modify a known compound in a particular manner," the rejection is improper. Accordingly, Applicants respectfully request withdrawal of the rejection.

(b) The '713 Patent

Claims 23, 27, 28, 31-33, 36, 37, and 40-42 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,922,713 ("the '713 patent") to Werner for the reasons set forth in the Office Action at page 23. Specifically, the Office alleges that the '713 patent "describ[es] pteridine compounds...for inhibition of nitric oxide synthase." Office Action at page 23. The Office notes "especially the compounds of [the '713 patent] in claims 10-13...[and] the compounds of Table I...that [the '713 patent] acknowledges to be known in the prior art that bind nitrix oxide synthase." *Id.* The Office concludes that the '713 patent "render[s] obvious lower alkyl homologs and positions isomer thereof." *Id.* The Office asserts that "[t]he skilled chemist would be well motivated to prepare other compounds and their compositions homologous and isomeric with those of [the '713 patent] according to the procedures taught therein with the expectation that such compounds would have the same herbicidal activity." *Id.* The Office also claims that "the skilled practitioner would also be motivated to use such homologous and isomeric compounds and their compositions in methods of treating a disorder associated with an increased nitric oxide level." *Id.* Applicants respectfully traverse.

As discussed above, compounds that are structurally homologous to those in the prior art, without more, are not *prima facie* obvious. As noted in M.P.E.P. § 2144.09(II),

"[h]omology should not be automatically equated with *prima facie* obviousness." Indeed, the Federal Circuit has recently indicated that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." *Takeda Chemical Ind. Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007) (internal citations omitted, underlining added). The Office has not complied with this requisite.

Moreover, with the amendments provided herein, claims 27, 32-33, 36, 37, and 40-42 have been canceled making the rejection of these claims moot. Currently amended claim 23 limits, among other things, R_{11} to an optionally substituted $(C_1\text{-}C_5)$-alkyl. Claims 28 and 31 depend upon claim 23 and thus, encompass this same limitation. The '713 patent, by contrast, discloses only compounds bearing a hydrogen at the R_{11} position. Further, the formula in claims 1 and 10 of the '713 patent allows for a double bond at the 7-8 position of the pteridine ring system, thus eliminating any possible substituent at the R_{11} position. Finally, neither the Office nor EP '913 provide a reason to modify at R_{11} at all, let alone to an optionally substituted $(C_1\text{-}C_5)$-alkyl. Because the Office has not complied with the explicit requirement enunciated in *Takeda* "to identify some reason that would have led a chemist to modify a known compound in a particular manner," the rejection is improper. Accordingly, Applicants respectfully request withdrawal of the rejection.

V. Obviousness Double Patenting

Claims 32-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 20-42 of U.S. Patent Application No. 10/549,200 ("the '200 application") for the reasons set forth in the Office Action at page 24. Specifically, the Office alleges that "there is significant overlap between claims 20-42 of [the '200 application] and the instant claims 32-42." Office Action at page 24. The Office further asserts that "[a]lthough the claims of [the '200 application] state that they are directed to a method of treating a subject having an increased intracranial pressure, while the claims of the present application state that they are directed to a method of treating a disorder associated with an increased nitric oxide level, both sets of claims involve the same steps of administering 2,4-diamino-7,8-dihydropteridines that inhibit nitric oxide synthase." *Id.* Applicants respectfully traverse. Nonetheless, solely to expedite prosecution, Applicants have deleted claims 32-42 herein. As such, Applicants respectfully request withdrawal of the rejection.

VI. Conclusion

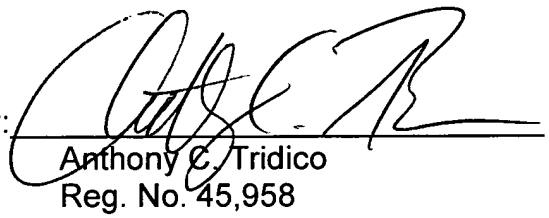
In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 19, 2008

By: 
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